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14. ABSTRACT

The purpose of the series of experiments carried in this ASSERT Award was to determine how dopamine agonists would affect the acoustic startle reflex. We found that dopamine agonists increase the acoustic startle reflex by acting at dopamine, D1 receptors in both the striatum and the substantia nigra zona reticula (SNr). The SNr projects via a GABAergic pathway to the deep layers of the superior colliculus which in turn projects to the acoustic startle pathway. Activation of dopamine receptors in the dorsal striatum and SNr leads to a release of GABA in the SNr which inhibits the GABA neurons that project to the deep layers of the superior colliculus. This produces a disinhibition of these neurons and a consequent increase in the acoustic startle reflex. The work is relevant to how dopamine acts on motor reflexes as well as the role of dopamine in attention.

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1. Enhancement of the acoustic startle response in rats by the dopamine D_1 receptor agonist SKF 82958

The present series of experiments were conducted in order to assess the nature of dopaminergic modulation of the acoustic startle response in male Sprague-Dawley rats using agonists and antagonists specific for dopamine D_1 and D_2 receptors. Systemic administration of the high-efficacy dopamine D_1 receptor agonist SKF 82958 (.01, 0.1, 1 and 3 mg/kg, s.c.) produced a dose-dependent enhancement of startle across a range of intensities (80-115 dB) that was both subthreshold and suprathreshold for startle evocation. Systemic administration of a second D_1 receptor agonist, SKF 81297 (3 mg/kg), also produced a marked enhancement of startle suggesting that this effect is dependent on D_1 receptor activation. Systemic pretreatment with the D_1 receptor antagonist SCH 23390 (.01 and 0.1 mg/kg) produced a dose-dependent blockade of the enhancement of startle by SKF 82958 (1 mg/kg) whereas pretreatment with the D_2 receptor antagonist raclopride (0.1 and 1 mg/kg) dose-dependently blocked the enhancement of startle by SKF 82958 at the subthreshold intensities (80 and 85 dB) and attenuated the enhancement at suprathreshold intensities (90, 95, and 100 dB). These data suggest a cooperative type of D_1/D_2 receptor interaction whereby D_2 receptor activation is necessary for the full expression of the D_1 receptor-mediated enhancement of startle.

2. Enhancement of the acoustic startle response by dopamine agonists after 6-hydroxydopamine lesions of the substantia nigra pars compacta: corresponding changes in c-Fos expression in the caudate-putamen

Rats with 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal pathway show enhanced locomotor and stereotyped behaviors when challenged with direct and indirect dopamine (DA) agonists due to the development of postsynaptic supersensitivity. To determine if this phenomenon generalizes to other motor behaviors, we have used this rat model of Parkinson's disease to examine the effects of the direct dopamine D_1 receptor agonist SKF 82958 and the indirect DA agonist L-3,4-dihydroxyphenylalanine (L-DOPA) on the acoustic startle response. In addition, we used the expression of c-Fos protein as a marker of neuronal activity to assess any corresponding drug-induced changes in the caudate-putamen (CPu) after L-DOPA administration. Male Sprague-Dawley rats received bilateral injections of 6-OHDA into the substantia nigra pars compacta and one week later were tested for startle after systemic administration of SKF 82958 (0.05 mg/kg) or L-DOPA (1, 5, 10 mg/kg). SKF 82958 produced a marked enhancement of startle with a rapid onset in 6-OHDA-lesioned but not SHAM animals. L-DOPA produced a dose- and time-dependent enhancement of startle in 6-OHDA-lesioned rats that had no effect in SHAM animals even at the highest dose (10 mg/kg).

Furthermore, L-DOPA produced a dramatic induction of c-Fos in the CPu in 6-OHDA-lesioned animals. Consistent with other literature, these data suggest that neurons in the CPu become supersensitive to the effects of DA agonists after 6-OHDA-induced denervation of the nigrostriatal pathway and that supersensitive dopamine D_1 receptors may mediate the enhancement of startle seen in the present study.

3. The substantia nigra pars reticulata mediates the enhancement of startle by the dopamine D_1 receptor agonist SKF 82958 in rats

To test the involvment of the substantia nigra pars reticulata (SNr) in the enhancement of startle by dopamine agonists, male Sprague-Dawley rats were implanted with cannulas into the SNr and one week later infused with either the D_1 antagonist SCH 23390 (0.1, or 1 μg) or the $GABA_A$ antagonist bicuculline (0.1 μg) followed by a systemic challenge with the D_1 agonist SKF 82958 (1 mg/kg). Both SCH 23390 and bicuculline completely blocked the enhancement of startle by SKF 82958. Other rats were infused with the $GABA_A$ agonist muscimol (0.1 μg) or SKF 82958 (0.1, 1, or 5 μg). Muscimol produced a significant increase in startle whereas SKF 82958 had no effect. These results suggest that activation of D_1 receptors in the SNr is necessary for the enhancement of startle by SKF 82958 but that activation of these receptors alone is not sufficient to produce this response. These results also suggest that GABA transmission in the SNr may be involved in the enhancement of startle by SKF 82958. Based on these data, we propose that activation of striatonigral neurons by D_1 receptor agonists facilitates GABA release in the SNr to enhance startle.

4. GABA in the deep layers of the superior colliculus/mesencephalic reticular formation mediates the enhancement of startle by the dopamine D_1 receptor agonist SKF 82958 in rats

GABA transmission in the deep layers of the superior colliculus/deep mesencephalic reticular formation (deep SC/Me) mediates several motor responses, including those expressed after systemic administration of dopamine agonists. In the present study, we examined the role of the deep SC/Me in the modulation of the acoustic startle reflex and its enhancement by the dopamine D_1 agonist SKF 82958. Rats were implanted with bilateral cannulas into the deep SC/Me or superficial layers of the SC (super SC) and one week later infused with various compounds. The $GABA_A$ antagonist bicuculline (0, 5, 10 ng) produced a dose- and time- dependent enhancement of startle after infusion into the deep SC/Me but not the super SC. Infusion of the $GABA_A$ agonist muscimol (0.1 μg) into the deep SC/Me but not the super SC blocked the enhancement of startle by systemic SKF 82958 (1 mg/kg) but had no effect on baseline startle by itself.

This effect was not produced by infusion of the D_1 antagonist SCH 23390(1 μg) or the glutamate antagonist NBQX (1 μg). Deposits of Fluoro-Gold into the deep SC/Me combined with immunohistochemistry for glutamic acid decarboxylase (GAD) confirmed a direct GABAergic input from the substantia nigra pars reticulata (SNr) to the deep SC/Me. These results suggest that GABA tone in the deep SC/Me modulates the expression of startle as well as the enhancement of startle by dopamine D_1 agonists. Based on these data and previous work, we have proposed a striatonigral-tectal-reticular neural pathway mediating the effects of dopamine D_1 agonists on startle.